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How Frequent is Chronic Multiyear Delusional Activity and Recovery in Schizophrenia: A 20-Year Multi–follow-up

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To determine how frequent chronic multiyear delusional activity is in modern-day schizophrenia, we studied 200 patients over a 20-year period. We also studied the relation of delusions to hallucinations and thought disorder-disorganization, to work disability, and to later periods of global recovery and assessed several protective factors against delusional activity. The sample was assessed 6 times over 20 years and includes 43 patients with schizophrenia. Participants were evaluated at each follow-up for delusions, hallucinations, thought disorder-disorganization, work disability, and global recovery. Possible protective factors were assessed prospectively at index hospitalization. Twenty-six percent of the patients with schizophrenia were delusional at all follow-ups over the 20 years. Overall, 57% had frequently recurring or persistent delusions. A subgroup of over 25% of the schizophrenia patients had no delusional activity at any of the 6 follow-ups over 20 years. Schizophrenia patients with posthospital delusional activity had increased work disability ($P < .05$). Delusions that persisted after the acute phase in schizophrenia patients predicted a lower likelihood of future global recovery ($P < .01$). In conclusion, slightly over half of modern-day schizophrenia patients are vulnerable to frequent or "chronic" delusional activity after the acute phase. Schizophreniform patients and other types of psychotic disorders are vulnerable to posthospital delusional activity, but less frequently, less severely, and more episodically. Delusional activity is associated with work disability. Internal factors such as good premorbid developmental achievements and favorable prognostic factors are protective factors that reduce the probability of chronic multiyear, delusional activity in schizophrenia ($P < .01$).

Key words: chronic/delusions/recovery/schizophrenia/followup/work disability/hallucinations/thought disorder-disorganization/outcome/prognosis/community functioning

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How Frequent is Chronic Multiyear Delusional Activity and Recovery in Schizophrenia: A 20-Year Multi–follow-up

How frequent is chronic multiyear delusional activity in modern-day schizophrenia and schizophreniform disorders, and what are the consequences of vulnerability to frequent delusional activity in regard to work disability and subsequent recovery? Delusions and persistent or recurrent delusional activity have long been viewed as being among the central symptoms of schizophrenia[1–3] with much of our efforts and medication treatment centered on the reduction of psychotic activity.[4] However, longitudinal multi–follow-up data on how many or what percent of modern-day schizophrenia patients have persistent delusions and what percent do not experience any delusional activity over a multiyear period are relatively scant.[5–14] The current article provides this information by reporting multi–follow-up data on delusional activity over a 20-year period in schizophrenia, schizophreniform, and other types of psychotic disorders and explores the relation of delusions to work disability and later periods of global recovery. It also studies several variables that may be protective factors against frequently recurring delusional activity in schizophrenia.

Views by Kraepelin,[15] Bleuler,[16] and other early theorists emphasized the frequent or continuous positive symptoms experienced by patients with schizophrenia. Modern views, as exemplified by *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV)*, note that many patients with schizophrenia remain "chronically ill."[1] Although this characteristic is closely linked to the basic concept of schizophrenia, neither *DSM-IV* nor other authoritative views have systematically examined how frequently this type of "chronic" course occurs. Conversely, a related issue of importance for recent focus on potential global recovery in schizophrenia is whether some or many patients with schizophrenia experience periods with little or no recurrent delusions over an extended period.

Two important issues concerning the pathology involved in schizophrenia are the prominence of work disability and the factors that contribute to it, and the even larger issue of potential global recovery for patients with schizophrenia. Some recent evidence has suggested that delusions do not play an important role in work disability in schizophrenia.[17,18] The present research using a longitudinal framework studied whether delusional activity increases work disability and whether the presence of delusions after the acute phase of hospitalization indicates greater vulnerability and few subsequent periods of global recovery. It also studied the relation of delusional activity to other positive symptoms such as hallucinations and thought disorder-disorganization (TD).

While delusions are one of the central symptoms in schizophrenia, they also play a role in other types of psychotic disorders. However, precise data are not available on whether patients with schizophreniform or other types of psychotic disorders are vulnerable to subsequent delusional episodes after the original acute phase.[19,20] If one uses a stress-diathesis model[21–25] for both schizophrenia patients and patients with other types of psychotic disorders, one might expect that patients with other types of psychotic disorders (who already showed vulnerability to delusions at the acute phase) also have some genetic-biological vulnerability to delusional activity. With this diathesis, one might expect that some or many patients with other types of psychotic disorders also show vulnerability to delusions after the acute phase.

Another factor of considerable importance is identifying the protective factors that may increase the probability of patients with schizophrenia experiencing less delusional activity over a prolonged period.[4] A number of modern theorists have begun to study cognitive factors that may be involved in delusional activity.[2,26–35] The present research examines several factors internal to the patient that have the potential to identify the characteristics of the subgroup of schizophrenia patients with little or no delusional activity over a prolonged period.

Overall, in this longitudinal research the following questions were addressed:

1. How vulnerable are modern-day patients with schizophrenia to frequently recurring or continuous delusional activity when assessed longitudinally? Is there a strong link between delusions and hallucinations in schizophrenia?
2. Is there a subgroup of modern-day patients with schizophrenia who show little or no delusional activity when assessed longitudinally?
3. Is delusional activity one of the factors contributing to work disability in schizophrenia?
4. For those schizophrenia patients whose delusions persist after the acute phase of hospitalization, does this indicate a more severe vulnerability to psychotic activity, fewer periods of global recovery, and a poorer subsequent prognosis over a mutiyear period?
5. Are patients with schizophreniform disorders and with other types of psychotic disorders vulnerable to delusional activity after they recover from their acute phase delusional episode?
6. Can one identify characteristics of schizophrenia patients that serve as protective factors and are associated with little or no delusional activity over a prolonged period?

Methods

Patient Sample

The current investigation is based on data from the Chicago Follow-up Study, a prospectively designed, longitudinal, multi–follow-up research program studying major symptoms (including psychosis, negative symptoms, and TD), outcome, recovery, and factors involved in psychopathology and recovery in schizophrenia and other types of psychotic disorders.[36–41] Two hundred young patients, relatively early in their illness, were studied prospectively at the acute phase of hospitalization and then reassessed at 6 subsequent follow-ups over a 20-year period. The follow-ups occurred at 2, 4.5, 7.5, 10, 15, and 20 years posthospital.

The sample of 200 patients included, using *Diagnostic and Statistical Manual of Mental Disorders (Third Edition)* criteria, 43 patients with schizophrenia, 10 schizophreniform patients, 66 other types of psychotic disorders (including 29 bipolar patients, 23 unipolar psychotic depressive patients, and 14 patients with other types of psychotic disorders), and a control sample of 81 nonpsychotic patients (including 51 unipolar nonpsychotic depressive patients). After Institutional Review Board approval, signed informed consent was obtained from all subjects. The research diagnoses were based on structured research interviews conducted during index hospitalization, supplemented by intake interviews at hospital admission. The research interviews consisted of at least one of 2 structured interviews: (1) the Schedule for Affective Disorders and Schizophrenia (SADS)[42] and/or (2) the Schizophrenic State Inventory, with each interview being tape-recorded.[43] Satisfactory interrater reliability was established for diagnosis (eg, a kappa of 0.88 for schizophrenia).

The mean age of the patients at index hospitalization was 23 years and at the 20-year follow-ups was 43.4 years. The ages did not differ across diagnoses. The mean level of education at index was 13 years. Fifty-one percent of the patients were male, with more of the schizophrenia patients being males and more of the nonpsychotic depressives being females. Recent evidence indicates that this type of sex ratio difference is typical for early young patients with schizophrenia who have been

hospitalized.[44] Fifty-five percent of the sample were first admission patients at index, and another 21% were second admission patients. Thus, 76% were either first or second admission patients. All 200 patients were studied prospectively at index hospitalization and at the 20-year follow-ups. One hundred ten of the 200 patients were studied at all 6 follow-ups over the 20 years, and another 62 patients were studied at 5 of the 6 follow-ups. Diagnostically, among the sample of 200 patients we were able to assess at 5 or all 6 follow-ups over 80% of the patients from each of the 3 main groups. This included the patients with schizophrenia, those with other psychotic disorders, and those with nonpsychotic disorders, with no diagnostic differences in the rate of follow-ups. Information on outcome at the 20-year follow-ups was available for 73% of the original sample assessed. The 43 patients with schizophrenia in the current research were compared with a subsample of schizophrenia patients who were assessed at index hospitalization and at the first follow-ups but who were not reassessed at the 20-year follow-ups. The 2 groups did not differ, significantly, on major demographic variables or on scores on delusional activity at the 2-year follow-ups.

Follow-up Evaluations and Assessment of Delusions, Other Positive Symptoms, and Work Functioning

The follow-up evaluations involved an established protocol that included a structured interview on symptoms, a structured interview on functioning, and performance tests, including 3 tests to derive a composite index of TD. The follow-up interviews and ratings were conducted by trained raters who were not informed of diagnosis. Patients were assessed at each follow-up for positive and negative symptoms, for affective syndromes, on work and social functioning, on global outcome and potential recovery, and on treatment.

Delusions and hallucinations at each follow-up were assessed with the SADS.[42] Delusions were rated on 3-point scales as follows: 1 = delusion absent; 2 = weak or equivocal delusion; 3 = full delusion present.[45] Hallucinations were rated separately on a similar 3-point scale designed to assess the strength of hallucinations.[46] In regard to delusions, our SADS covers the occurrence within the past month and past year of 16 individual types of delusions.[47] Because patients are usually regarded as delusional regardless of whether they show clear delusions in one or in several areas, a single composite rating of the 16 delusional categories was made based on the highest score for each patient on any given type of delusion.

TD was assessed using a comprehensive index scored from a battery of 3 tests: the Gorham Proverbs Test,[48] the Goldstein-Scheerer Object Sorting Test,[49] and the comprehension subtest of the WAIS.[50] TD was scored on the 3 tests based on qualities associated with formal thought disorder such as loose associations, illogical or autistic thinking, incoherent speech, and bizarre or strange expressions. The scoring system is described in a detailed manual[51]. Good internal consistency and adequate reliability of the index has been obtained, the TD index discriminates patient groups with schizophrenia and mania from other groups, has been assessed longitudinally, and has been used in a number of reported studies[51–59].

To assess work functioning, a scale designed by Strauss and Carpenter and used in a number of previous studies was employed.[40,41,43,55,60,61] This 5-point scale, scored from questions on the functioning interview was scored as follows: "4" "employed" continuously; "3" "employed" more than half of the year, but less than continuously; "2" "employed"' part-time or full-time about half the time in the past year; "1" "employed" less than half the time in the past year, "0" no useful work.

Recovery

The criteria for global "recovery" during a follow-up year, defined operationally, required no positive or negative symptoms, and no rehospitalizations during the follow-up year. Also required were partially adequate (or better) work and social functioning (scores of "2" or greater on the Strauss-Carpenter scales).[60]

Early Prognostic Potential and Premorbid Developmental Achievements

Two important measures, assessed prospectively at index hospitalization, provided indices of early prognostic potential and premorbid development achievements of the schizophrenia patients. These measures could be viewed as tapping early risk and protective factors for later delusional activity.

One measure is a composite index of prognostic potential. This index is derived from factors outlined in the research of Vaillant,[62,63] of Stephens,[64,65] and others.[66] The good prognostic factors assessed prospectively at index hospitalization included an acute onset, precipitating stress at index, adequate work and social adjustment before index, preoccupation with death, the presence of depressive symptoms, confusion, guilt, being married, and no blunted affect.

The other measure, the Zigler-Phillips Scale, is an index of premorbid developmental achievements. This scale has been applied to developmental theory, adult psychopathology and outcome, medication status, self-image, and to mental retardation.[35,67–69] The scale is based on patients' work history, education, marital status, age at first break, and IQ.

Medications

Data on medications are presented in the "Results" section.

Results

Vulnerability of Patients With Schizophrenia and Other Psychotic Disorders To Delusional Activity Over the 20-Year Period

Figure 1 reports the course of delusional activity at 6 follow-ups over 20 years for patients with schizophrenia vs patients from the other psychotic and nonpsychotic patient groups. A 4 × 6 mixed design, repeated-measures analysis of variance (4 diagnostic groups and 6 follow-up assessments) showed large significant diagnostic differences ($F = 18.69$, $df = 3, 106$, $P < .001$), with schizophrenia patients having more delusional activity. Separate analyses comparing the schizophrenia patients with the patients with other types of psychotic disorders on delusional activity showed the schizophrenia patients as having significantly more delusional activity at 5 of the 6 follow-ups ($P < .05$). There also was a significant effect for time ($F = 2.92$, $df = 5, 530$, $P < .02$) with less delusional activity at the 15- and 20-year follow-ups than at the 2-year follow-ups. There was not a significant interaction ($F = 0.50$, $df = 15, 530$, NS).

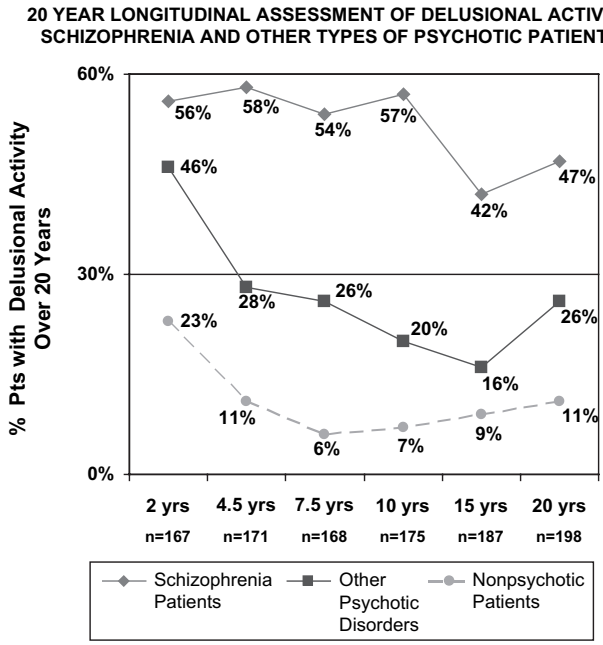

Fig. 1. Twenty-Year Longitudinal Assessment of Delusional Activity: Schizophrenia and Other Types of Psychotic Patients.

Vulnerability to Frequently Recurring or Persistent Delusions Over the 20-Year Period

Figure 2, based on the 86% of the patients with 5 or 6 follow-ups, presents the results on what percent of patients with schizophrenia experienced delusional activity at all follow-ups assessed over the 20 years, vs those with frequently recurring delusional activity over the 20-year period (ie, showing delusional activity at 3 or more of the follow-ups), vs those with less frequent delusional activity and those with no delusional activity during the follow-up years over the 20-year period.

The data indicate that 26% of the patients with schizophrenia had delusional activity at all follow-ups over the 20-year period. When the sample of schizophrenia patients with delusional activity at all follow-ups and the additional 31% of schizophrenia patients with frequently recurring delusions are combined, slightly over half (57%) of the schizophrenia patients formed a subgroup with frequently recurring or persistent delusions. Significantly more of the schizophrenia patients than of the patients with other types of psychotic disorders (57% vs 24%) had frequently recurring or persistent delusions ($\chi^2 = 9.88$, 1 *df*, $P = .001$). However (figure 2), the great majority (over 70%) of patients with other types of psychotic disorders, in addition to their delusional activity at the acute phase, also experienced at least some delusional activity after the acute phase.

For the initially nonpsychotic patient group, delusional activity over the 20-year period was considerably less frequent and less severe. Fitting with their lower vulnerability in this area, 66% of these initially nonpsychotic patients showed no evidence of delusional activity over the 20-year period. None of them were continuously delusional, and only 8% showed frequent delusional activity.

Severity of Delusional Activity

There were group differences in the severity of psychotic symptoms. Among the subgroup of patients with delusional activity at a particular follow-up, a larger percent

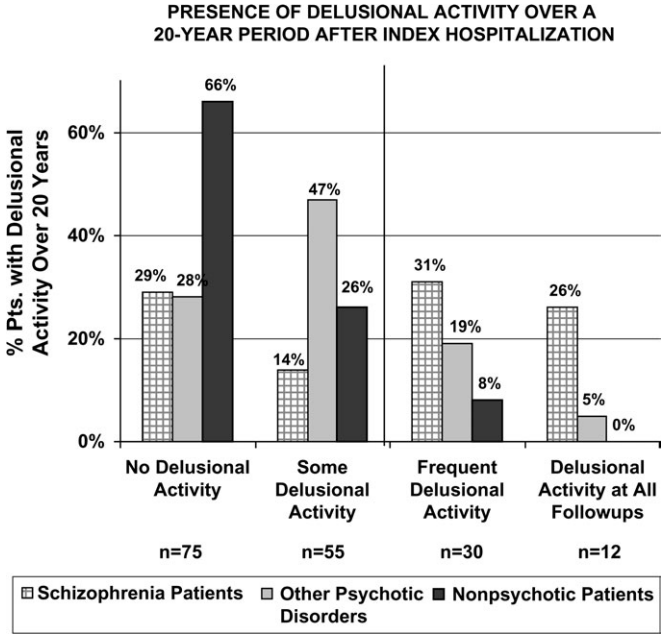

Fig. 2. Presence of Delusional Activity Over a 20-Year Period After Index Hospitalization.

of the schizophrenia patients than of the other psychotic disorders had full delusions in separate comparisons at each of the 6 follow-ups. In contrast to the weak or equivocal delusions (which were scored a "2"), these full delusional beliefs (assigned a score of "3") were held firmly by the patients, they were not infrequent or weak, and the patients did not have good perspective on them. These full delusional beliefs were, however, often not as flagrant as those held at the acute phase of hospitalization. The differences in severity between schizophrenia patients and other psychotic patients were significant at the 2-year follow-ups (χ^2 = 6.06, 1 *df*, P = .01) and at the 4.5-year follow-ups (χ^2 = 7.30, 1 *df*, $P < .01$).

Schizophrenia Patients With Little or No Posthospital Delusional Activity

There was a subgroup of 29% of the schizophrenia patients with no delusional activity at any of the 6 follow-ups over 20 years (see figure 2). Some of these patients had other problems (eg, social or work disability), but others were functioning adequately and experiencing a period of recovery.[41] Consistent with other research indicating a relationship between psychosis and work disability,[40,61] the majority of these patients (70%) were working full-time during at least 3 of their 6 follow-ups.

Medications

As frequently found in the natural clinical course of outpatients, there was no single, uniform treatment plan that applied to all patients. At the 20-year follow-ups, 65% of the schizophrenia patients were on psychiatric medications, with this including 54% on antipsychotic medications. At the 20-year follow-ups, 56% of the patients with other types of psychotic disorders were on psychiatric medications, including 29% on antipsychotics.

The current results and data from other studies suggest that some schizophrenia patients not on antipsychotics function well for a period of time.[35,37,70,71] Data by Fenton and McGlashan,[72] other data from our earlier studies,[37,38] and more recent data[35,41] suggest some distinct characteristics of the schizophrenia patients who do well after discontinuing antipsychotic medications. They had better premorbid developmental achievements and more favorable prognostic characteristics 20 years before, at index hospitalization, prior to the initiation of posthospital treatment, and are more resilient and less vulnerable to psychopathology leading to their better functioning and lower rate of posthospital psychosis.[35] Like most other medical disorders, where many of the favorable responders no longer feel they need treatment and eventually leave treatment, many of the subsample of schizophrenia patients who are functioning well eventually leave treatment. Hence, a larger percent of the schizophrenia patients not in treatment were experiencing a period of recovery than those on antipsychotics at the 15-year follow-ups (χ^2 = 9.81, 1 *df*, $P < .01$) and the 20-year follow-ups (χ^2 = 12.99, 1 *df*, $P < .001$).[35,41] Patients with schizophrenia who were not in treatment generally had less delusional activity than those on antipsychotic medications at the 15-year follow-ups (χ^2 = 2.20, 1 *df*, $P < .15$) and at the 20-year follow-up (χ^2 = 5.12, 1 *df*, $P < .05$). This type of schizophrenia patients who have left the mental health care–taking system for a sustained period of time are not usually included in most studies because they are not easy to locate or recruit for research,[35] and their long-term course is typically not evaluated.

Table 1. Delusional Activity: Correlations Over Time

Correlations Between Successive Follow-ups	Schizophrenia Patients	Other Types of Psychotic Disorders
2 *r* 4.5 y	0.78***	0.26†
4.5 *r* 7.5 y	0.71***	0.45***
7.5 *r* 10 y	0.83***	0.57***
10 *r* 15 y	0.61***	0.58***
15 *r* 20 y	0.54***	0.33**

†$P < .10$, *$P < .05$, **$P < .01$, ***$P < .001$.

Consistency of Delusional Activity Over Time and Its Presence as a Predictor of Subsequent Delusional Activity

Table 1 reports the correlations between delusional activity at successive follow-ups, 2.5–5 years later, for the patients with schizophrenia and for those with other types of psychotic disorders. The correlations at successive follow-ups years later were very high for the patients with schizophrenia ($P < .001$). The tendency for both of these groups was for patients who were vulnerable to delusional activity at one follow-up to be delusional at the next follow-up ($P < .05$), although (see table 1) this tendency was stronger for the schizophrenia patients.

Recovery Over Time From Delusional Activity: Patients With Schizophrenia and With Other Types of Psychotic Disorders

The schizophrenia patients with delusional activity at a follow-up were compared with patients from the other psychotic disorder group who had delusional activity at that follow-up on the likelihood of improvement (ie, no delusional activity) at the next follow-up years later.

These diagnostic comparisons of improvement over time indicated a tendency at each follow-up for comparatively greater improvement at the next follow-up for the other psychotic disorder group than for the schizophrenia patients. This greater improvement at the next follow-up for the other psychotic disorder group vs the schizophrenia patients was significant at the 4.5- vs the 2-year follow-ups (χ^2 = 13.56, 1 *df*, $P < .001$) and at the 10- vs the 7.5-year follow-ups (χ^2 = 6.68, 1 *df*, P = .01).

The slower recovery of the schizophrenia patients vs the other psychotic disorders points to their greater vulnerability to chronic delusional activity.

Relation Between Postacute Delusional Activity and Both Work Disability and Subsequent Periods of Global Recovery

Figure 3 reports data on the relationship between delusional activity and work disability for patients with schizophrenia at the 15- and 20-year follow-ups. Overall, there were strong significant differences in work performance between delusional and nondelusional schizophrenia patients at the 10-year follow-ups ($\chi^2 = 9.21$, 1 *df*, $P < .01$), the 15-year follow-ups ($\chi^2 = 10.98$, 1 *df*, $P < .001$), and the 20-year follow-ups ($\chi^2 = 7.04$, 1 *df*, $P < .01$). Over half of the schizophrenia patients who did not have delusional activity were working more than half time at the 4.5-, the 10-, the 15-, and at the 20-year follow-ups. In contrast, among the schizophrenia patients with full delusional activity at a follow-up, at 5 of the 6 follow-ups 10% or fewer were working more than half time.

Figure 4 reports the relationship between delusional activity at the 2-year follow-ups and global recovery over the next 18 years. The data indicate that schizophrenia patients without delusional activity at the 2-year follow-ups were more likely to experience one or more periods of global recovery over the next 18 years ($\chi^2 = 7.77$, 1 *df*, $P < .01$). One view of these data is that the persistence of delusions for the first few posthospital years for the schizophrenia patients may be an index of their vulnerability to psychosis and their lower potential for future periods of global recovery.

Relationship Between Delusional Activity and Both Hallucinations and TD

Table 2 reports the relationship at each of 6 follow-ups over 20 years between delusional activity and 2 other major types of positive symptoms, hallucinations and TD. Not surprisingly, the correlations between delusions and hallucinations were all extremely high with all 6 correlations over a 20-year period achieving significance at $P < .001$.

The correlations between delusions and TD for the schizophrenia patients were at the $r = 0.30$ level or higher at 3 of the 6 time frames assessed over the 20-year period. However, only the correlation at the 2-year follow-ups was statistically significant ($r = 0.53$, $P < .01$). Overall, the data indicate an extremely strong relationship at multiple follow-ups between delusions and hallucinations and some (but a limited one) relationship over time between delusional activity and TD.

The contribution of hallucinations or anomalous perceptual experiences to delusions have been proposed by a number of investigators and looked at conversely the potential contribution of delusional thinking to hallucinations can be posed. Table 3 provides data bearing on this issue in terms of the percent of hallucinating schizophrenia patients who are delusional and also the percent of delusional schizophrenia patients who are hallucinating. Consistent with the very high correlations reported in table 2 between these 2 types of psychotic phenomenon, table 3 indicates that a very high percent of schizophrenia patients with either delusions or hallucinations also showed the other type of psychotic phenomenon as well.

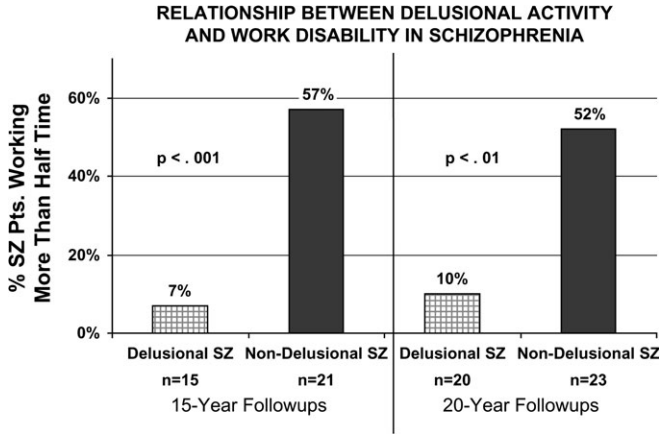

Fig. 3. Relationship Between Delusional Activity and Work Disability in Schizophrenia.

Delusional Activity Over Time in Schizophreniform Patients

The frequency of delusional activity for the schizophreniform patients, on an overall basis, was better (less frequent) than that of the schizophrenia patients and

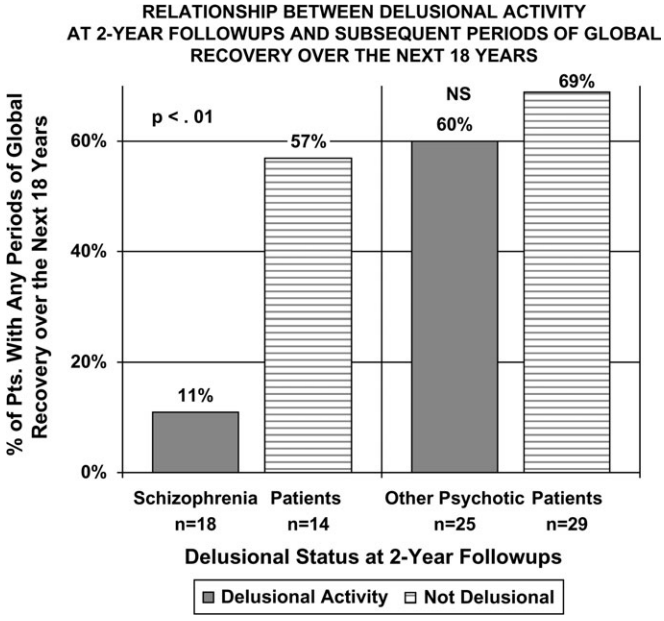

Fig. 4. Relationship Between Delusional Activity at 2-Year Follow-ups and Subsequent Periods of Global Recovery Over the Next 18 Years.

Table 2. Relation Between Delusions and Hallucinations and Thought Disorder-Disorganization Over 20 Years for Patients With Schizophrenia

Follow-up Period (y)	Delusions *r* Hallucinations	Delusions *r* Thought Disorder-Disorganization
2	0.85***	0.53**
4.5	0.85***	0.10
7.5	0.75***	0.32†
10	0.72***	0.32†
15	0.55***	0.17
20	0.53***	0.24

†$P < .10$, *$P < .05$, **$P < .01$, ***$P < .001$.

poorer (more frequent) than that of the other types of psychotic and nonpsychotic disorders. Overall, 90% of them showed at least some recurrence of delusional activity over the 20-year period. The delusional activity was, in general, less severe and less frequent, or more episodic, than that of the schizophrenia patients. None of the schizophreniform patients were delusional at all follow-ups, and only 29% of them showed frequent delusional activity. Thus, the schizophreniform patients showed some vulnerability to delusional activity, but most experienced delusional activity at a few, or at only one, follow-up rather than persistently showing delusional activity over time.

Protective Factors That May Contribute to Reduced Delusional Activity

Figure 5 reports the data on the classical prognostic indices of Vaillant and Stephens as a predictor of frequently recurring delusional activity over the subsequent 20-year period.

Only 14% of the schizophrenia patients with good prognostic indices at index experienced frequent or continuous delusional activity over the 20 years of follow-ups. Seventy-three percent of the schizophrenia patients with poor prognostic indices at index experienced frequent or continuous delusional activity over the 20-year period ($\chi^2 = 7.98$, 1 *df*, $P < .01$).

Table 3. Co-occurrence of Delusions and Hallucinations Over 20 Years in Schizophrenia

Follow-up Period (y)	Schizophrenia Patients Who Are Hallucinating: % With Delusions	Schizophrenia Patients Who Are Delusional: % With Hallucinations
2	100	83
4.5	100	80
7.5	80	67
10	100	70
15	75	60
20	82	70

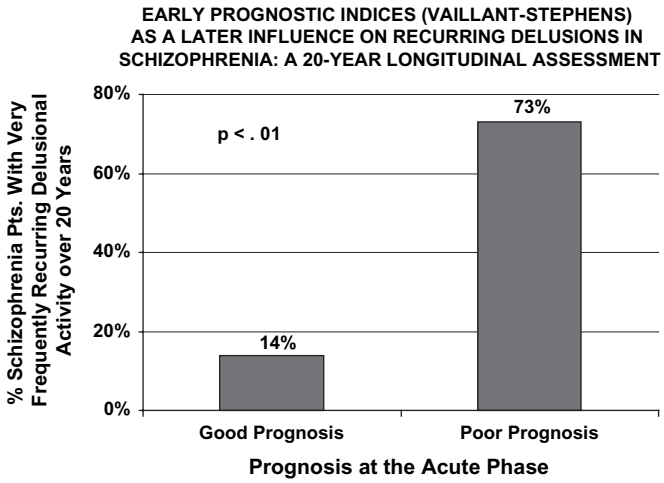

Fig. 5. Early Prognostic Indices (Vaillant-Stephens) as a Later Influence on Recurring Delusions in Schizophrenia: a 20-Year Longitudinal Assessment.

Using the Zigler scale,[67,68] there also were differences associated with premorbid developmental achievements. Significantly fewer of the schizophrenia patients with good premorbid developmental achievements had frequent or continuous delusional activity over the 20-year period than the schizophrenia patients with poor premorbid developmental achievements ($\chi^2 = 9.66$, 1 *df*, $P < .01$).

Discussion

The current research reports prospectively designed longitudinal data on delusional activity in modern-day patients with schizophrenia, with schizophreniform disorders, and with other types of psychotic disorders that have not previously been available to the field. Earlier views about basic differences between schizophrenia and other types of psychotic disorders emphasized persistent or very frequently recurring delusional activity as one of the defining symptoms of schizophrenia. The current longitudinal data provide evidence on a subgroup of modern-day schizophrenia patients who have frequently recurring or continuous delusions and another subgroup with little or no subsequent delusional activity over many years. It also provides data on differences in the course of delusional activity between patients with schizophrenia and those with other types of psychotic disorders, primarily with bipolar or unipolar mood disorders.

Vulnerability of Patients With Schizophrenia To Frequently Recurring or Persistent Delusional Activity

The data in figure 1 provide evidence that patients who were psychotic at the acute phase (ie, patients with schizophrenia and those with other types of psychotic disorders) are generally more vulnerable to some subsequent delusional activity. Cumulatively, a subgroup of about

25% of the schizophrenia patients showed delusional activity at all follow-ups assessed over the 20-year period. Applebaum et al,[5] using a much shorter time frame, reported similar results. Slightly over half of the current schizophrenia patients had frequently recurring or persistent delusional activity. These data, along with earlier data showing that at each follow-up from 40% to 60% of the patients with schizophrenia were manifesting some level of delusional activity, indicate that even after the acute phase, delusional activity is still a major problem for most modern-day patients with schizophrenia. Although less long-term institutionalization, earlier treatment and less stigma, as well as modern treatment and rehabilitative efforts provide a more optimistic outlook, patients with schizophrenia, as a group, still have more frequent or persistent and more severe delusional activity.

Continuity of Delusional Activity Over Time and Interference With Global Recovery

The very high correlations for delusional activity over time in the patients with schizophrenia (table 1) also bear on the issue of the greater vulnerability of these patients to delusional activity. These data fit in with the view that a moderate to large subgroup of schizophrenia patients are particularly vulnerable to delusional activity, and those schizophrenia patients with delusional activity at one follow-up are particularly likely to be experiencing it at the next follow-up many years later. Patients with other types of psychotic disorders also are vulnerable to delusional activity, but the lower frequency (figure 1), less severity, and lower correlations (table 1) over time would suggest that they are less vulnerable than schizophrenia patients.

Figure 4 provides evidence on the link between increased vulnerability to delusional activity and fewer subsequent periods of global recovery in schizophrenia. Thus, the correlational data in table 1 and the data in figure 4 suggest that positive symptoms still present a few years after the most recent acute phase tend to predict which schizophrenia patients are more likely to show later ''chronic'' difficulties in global adjustment. The persistence of delusions (usually at a lower level of severity) after the acute phase, which occurs in some, but not all, patients with schizophrenia may provide evidence of a more severe diathesis, often with a poorer long-term prognosis.

In regard to the severity of delusions, other data and theoretical views indicate that one factor involved in severity is the extent of ''emotional commitment'' by schizophrenia patients to their delusions,[40,45] with this often associated with acute episodes, when psychotic patients are ''profoundly immersed'' in their delusions.[73] Data on the importance of emotional commitment as one major factor in the severity of delusions[40,45,74,75] would fit with the views of Kapur and others[76–78] about the role of dopamine in mediating salience. A second factor of importance is a suspension of, or failure in, self-monitoring in select areas, with this involved in the patient's selective ignoring of previously learned consensual norms in the specific areas of the patient's unrealistic or delusional beliefs.[27,34,79]

Delusions and Work Disability

Previously there has been mixed evidence on the impact in schizophrenia of positive symptoms such as delusions on instrumental work functioning. An important review[17,18] has concluded that there is a strong relationship between work disability and neurocognitive impairment but little relationship between psychosis and work disability. Our own previous empirical research in this area has found evidence of a strong link between neurocognitive impairments and work disability,[80] but we also have reported evidence indicating a relationship between positive symptoms and work disability.[40,55,61,80]Additionally, we have found a significant relationship in schizophrenia between negative symptoms and work disability[81] as well as between depression and work disability.[82]

The above data and other very strong data on neurocognition[17] would lead to the conclusion that impaired neurocognition as well as multiple other factors (including major symptoms) can interfere with work functioning in schizophrenia. Considered from this viewpoint, impairments in multiple different areas, rather than only one area, would be candidates to interfere with work functioning and lead to work disability in schizophrenia. Of considerable importance, of some surprise, and providing hopeful indications, are the data indicating that after the earlier 2-year follow-ups, at the 4.5-, the 10-, the 15-, and the 20-year follow-ups slightly over half of the patients with schizophrenia who were not delusional were working over half time. In contrast, after the first 7 years, full delusional activity was strongly linked to work disability.

Community functioning is a key feature of outcome in schizophrenia. Work disability represents one important aspect of community functioning, and the data point to the importance of the interrelationship of both delusional activity and this aspect of community functioning in considering outcome in schizophrenia. Overall, work disability, as a key aspect of community functioning, represents one of the major problems associated with schizophrenia, both in terms of the economic cost to society and the emotional cost to individual patients. Eventual improved treatment methods concerning reduction of major symptoms in schizophrenia may be one path to reduction of work disability in these patients.

The Link Between Delusional Activity and Hallucinations

The data in tables 2 and 3 support views about the close relationship between delusions and hallucinations and

support other data about these 2 types of psychosis fitting in as a common factor over the years.[13,46,83–87] A major theoretical view that has been advanced is that delusions are partly due to patients trying to explain or deal with their own anomalous experiences or aberrant perceptual experiences and/or hallucinations[88] with empirical support for this for select people.[89] As an alternate possibility, almost the converse of the above view, one could propose the primacy of delusional thinking, with many or most full hallucinations in schizophrenia being based on patients' regarding them seriously because of their delusional-like thinking. Fitting in with this view, some "normal" people who are not delusional occasionally hear a voice calling their name or even a voice from a deceased love one calling to them or speaking to them. Most of these "normal" people do not have a delusional framework,[90] and are reality oriented, enabling them to recognize the voice as coming from their imagination and ignore it.

The data in table 3 could fit in with the view that hallucinations precipitate delusions, or delusions precipitate hallucinations. The very high percent of hallucinating patients who are also delusional (at several follow-ups it was 100%) could be interpreted as supporting views about the role of delusional thinking in making hallucinations seem more real or important to schizophrenia patients, although these data could be interpreted either way. The data indicating that some patients with schizophrenia were delusional without hallucinations would indicate that in schizophrenia delusions can occur without anomalous or hallucinatory experiences. However, the overall data from table 3 could be interpreted as indicating that either of these psychotic symptoms may play a role in the genesis of the other one. The 2 above views concerning the nature and genesis of psychotic factors are important ones. In general, the issue of how delusions and hallucinations may each contribute to the other one has not been fully explored and deserves further major research.[89]

In addition, there is a third strong possibility. This third possibility is that the patients with schizophrenia have a general vulnerability to reality distortions and to multiple types of psychoses, and this general vulnerability is responsible for both delusions and hallucinations. The outlook that a general vulnerability to reality distortions underlies the genesis of both hallucinations and delusions has a long history with concepts such as "anomalous experience,"[88,91] "heightened cognitive arousal,"[34,79] and altered salience.[76,77] The view here is that psychosis is not primarily the result of wrong ideas, beliefs, percepts, or cognitions but rather the transient distortion and poor self-monitoring of these phenomena by a separate system (possibly an affective, or salience producing system) that attributes aberrant significance to them.

This view is consistent with the evidence that during remission most psychotic persons regain coherence regarding the very ideas that previously constituted their delusion. Over time these alterations in cognition and perception can become very persistent even in some patients that are adequately treated with antipsychotic medications. If one adopts this outlook, the most important factor as to whether a given patient does or does not develop persistent psychotic symptoms is their level of vulnerability rather than life experience or medication history. The high correlations in table 2 and the data in table 3 would fit any of the above 3 possible views.

Patients With Other Types of Psychotic Disorders

The data provide further evidence that vulnerability to delusional activity during the posthospital period is not exclusive to schizophrenia. The great majority of patients with other types of psychotic disorders (most had mood disorders) also eventually reexperienced delusional activity. These data support previous results indicating that patients with initial psychotic bipolar and unipolar mood disorders also are vulnerable to subsequent delusional activity.[8,92]

The data, however, indicate that while patients with other types of psychotic disorders also are vulnerable during the posthospital period to delusional activity, they experience it less frequently and less severely and recover from delusional activity more quickly than patients with schizophrenia. In this sense, one might view the other psychotic disorders as having a less severe diathesis for delusional activity and/or as being more resilient than schizophrenia patients.

Results reported previously suggest that when bipolar and unipolar mood-disordered patients show positive symptoms at follow-up, it is during periods when many of them also are actively experiencing new affective syndromes.[53,92,93] This raises the issue of whether the set of vulnerability factors that predispose for delusions for schizophrenia patients target a different biological-genetic diathesis from those patients with other types of psychotic disorders.[94] An alternative is that the diathesis is fundamentally the same across diagnostic groups with only the degree of vulnerability constituting the distinguishing factor (ie, a more severe vulnerability for patients with schizophrenia).

The current results support data indicating that patients without schizophrenia who have psychotic mood disorders are more vulnerable on a longitudinal basis to experience delusional episodes than parallel samples of mood-disordered patients who do not have delusional activity at the acute phase (ie, unipolar nonpsychotic depressives).[92]

Schizophreniform Patients and Delusional Activity

Although schizophreniform disorders are categorized separately from schizophrenia, while viewed by some as schizophrenia spectrum disorders, there are only a limited

number of longitudinal studies of delusional activity of these patients.[19,20] More data in this area are needed. The results for the current sample suggest that the schizophreniform patients are vulnerable to delusional activity but not as vulnerable to chronic continuous delusions as the schizophrenia patients. The results provide support for the most prevalent view that the less chronic and shorter duration of onset at index of the schizophreniform patients is linked to a less severe underlying disorder for these patients than for the schizophrenia patients. Other longitudinal data have suggested that despite experiencing some adjustmental difficulty over the years, the schizophreniform patients are not as vulnerable to chronic sustained disorder as schizophrenia patients.[41]

Our data indicate that most of the schizophreniform patients represent a more-than-one episode disorder, but their delusional activity involved milder and infrequent periods and are more episodic rather than being a chronic problem. An additional factor that may have contributed some is that perhaps their reduction in symptom persistence also was influenced by their earlier engagement with psychiatric services, leading to a reduction in the duration of untreated psychosis. However, hypotheses about the exact impact of early treatment have not been resolved with finality.

Patients With Schizophrenia Who Experienced Little or No Delusional Activity During the 20-Year Posthospital Period and the Relevance of a Stress-Diathesis Model

One of the older views of schizophrenia is that all, or all but a few, patients with schizophrenia will have recurrences of delusional activity. However, the current 20-year longitudinal data suggest that after the acute phase there is a subgroup of over 25% of these patients who manifest little or no delusional activity over a prolonged period. Modern-day treatment, including the administration of antipsychotics to all patients during the acute inpatient phase and the use of antipsychotic medications during the follow-up period for some of these schizophrenia patients contributed to the lack of delusional activity. However, over half of these patients who did not show delusional activity were not on antipsychotic medications for most of the 20-year follow-up period, and a number of them had discontinued treatment altogether.[35]

Thus other factors, including some protective factors, would also seem to be involved. These protective factors include low vulnerability to anxiety in some schizophrenia patients, various cognitive factors, and other patient characteristics.[2,14,26,33,91,95–101] Further research to study these factors more precisely and the mechanisms involved would seem important.

The present data suggest that better premorbid developmental achievements and more favorable prognostic factors at index hospitalization may serve as protective factors against delusions in schizophrenia. The great majority of schizophrenia patients who showed no delusional activity had favorable scores on one or both of these indices. However, it is quite possible that a third factor that is related to both of these variables explains the associations. In addition, there are other potential protective factors, as well as other factors which influence outcome, some based on internal characteristics or biological features of patients with schizophrenia. Further research to identify these factors would seem important.

These data on delusional activity fit a stress-diathesis model for both patients with schizophrenia and for those with other types of psychotic disorders.[21–23,25] Both groups have an underlying diathesis that makes them vulnerable to delusional activity. The current data and that of others indicate that among these 2 groups of vulnerable patients, those with schizophrenia have a greater vulnerability than those with other types of psychotic disorders.[5,74] This latter finding could lend support to those who argue for an impaired neurocognitive brain circuit unique to patients with frequent psychotic activity[102–104] although more substantive evidence is needed in this area. Looked at from the opposite direction, that of protective factors, both good premorbid developmental achievements and favorable prognostic indices decrease the chances of the overt expression of delusional activity in otherwise vulnerable patients.

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References

1. American Psychiatric Association.*Diagnostic and Statistical Manual of Mental Disorders 4th Text Revision ed Washington, DC: American Psychiatric Association; 2000.*
2. Butler R, Braff D. Delusions: a review and integration. *Schizophr Bull*. 1991;17:633–647.
3. Thaker G, Carpenter W. Advances in schizophrenia. *Nat Med.* 2001;7:667–671.
4. Addington J, Cadenhead K, Cannon T, et al. North American prodrome longitudinal study: a collaborative multisite approach to prodromal schizophrenia research. *Schizophr Bull.* 2007;33:665–672.
5. Appelbaum P, Robbins P, Vesselinov R. Persistence and stability of delusions over time. *Compr Psychiatry*. 2004;45:317–324.
6. Astrup C, Noreik K, Elkes J. *Functional Psychoses: Diagnostic and Prognostic Models.* Springfield, Ill: Charles C. Thomas; 1966.
7. Harrow M, Carone B, Westermeyer J. The course of psychosis in early phases of schizophrenia. *Am J Psychiatry*. 1985;142:702–707.

8. Harrow M, McDonald A, Sands J, Silverstein M. Vulnerability to delusions over time in schizophrenia, schizoaffective and bipolar and unipolar affective disorders: a multi-followup assessment. *Schizophr Bull*. 1995;21:95–109.
9. Carpenter W, Strauss J. The prediction of outcome in schizophrenia IV: eleven-year follow-up of the Washington IPSS cohort. *J Nerv Ment Dis.* 1991;179:517–525.
10. Angst J. European long-term follow-up studies of schizophrenia. *Schizophr Bull.* 1988;14:501–513.
11. Harrison G, Hopper K, Craig T, et al. Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry*. 2001;178:506–517.
12. Tsuang M, Woolson R, Fleming J. Long-term outcome of major psychoses: I. Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. *Arch Gen Psychiatry*. 1979;36:1295–1301.
13. Arndt S, Andreasen N. A longitudinal study of symptom dimensions in schizophrenia. *Arch Gen Psychiatry*. 1995;52:352–360.
14. Harrow M, Jobe T, Astrachan-Fletcher E. Prognosis of persecutory delusions in schizophrenia: a 20-year longitudinal study. In: Freeman D, Garety P, Bentall R, eds. *Persecutory Delusions: Assessment, Theory and Treatment. Oxford: Oxford University Press; In press.*
15. Kraepelin E. *Dementia Praecox and Paraphrenia. Barclay R, trans.* New York, NY: Robert E Krieger Publishing Company Inc; 1971:1919.
16. Bleuler E. *Dementia Praecox or the Group of Schizophrenias. Zinkin U, trans.* New York, NY: International Universities Press; 1950. (Original work published in 1911).
17. Green M. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry*. 1996;153:321–330.
18. Green M, Kern R, Braff D, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the ''right stuff''? *Schizophr Bull.* 2000;26:119–136.
19. Poulton R, Caspi A, Moffitt T, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder a 15-year longitudinal study. *Arch Gen Psychiatry*. 2000;57: 1053–1058.
20. Cannon M, Caspi A, Moffitt T, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry*. 2002;59:449–456.
21. Nuechterlein K, Dawson M. A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophr Bull.* 1984;10:300–312.
22. Norman R, Malla A. Stressful life events and schizophrenia. 1: a review of the research. *Br J Psychiatry*. 1993;162:161–166.
23. Walker E, Diforio D. Schizophrenia: a neural diathesis-stress model. *Psychol Rev.* 1997;104:667–685.
24. Corcoran C, Walker E, Huot R, et al. The Stress cascade and schizophrenia: etiology and onset. *Schizophr Bull.* 2003;29:671–692.
25. Docherty N, St-Hilaire A, Aakre J, Seghers J. Life events and high-trait reactivity together predict psychotic symptom increases in schizophrenia. *Schizophr Bull.*[published online ahead of print January 31, 2008]. doi:10.1093/schbul/sbn002.
26. Bentall R, Corcoran R, Howard R, Blackwood N, Kinderman P. Persecutory delusions: a review and theoretical integration. *Clin Psychol Rev.* 2001;21:1143–1192.
27. Frith C, Geraint R, Friston K. Psychosis and the experience of self: brain systems underlying self-monitoring. *Ann N Y Acad Sci.* 1998;843:170–178.
28. Freeman D, Garety P, Kuipers E, Fowler D, Bebbington P. A cognitive model of persecutory delusions. *Br J Clin Psychol.* 2002;41:331–347.
29. Hoffman RE. Computer simulations of neural information processing and the schizophrenia-mania dichotomy. *Arch Gen Psychiatry*. 1987;44:178–188.
30. Kendler K. Heritability of schizophrenia. *Am J Psychiatry*. 1983;140:131.
31. Spitzer M. A neurocomputational approach to delusions. *Compr Psychiatry*. 1995;36:83–105.
32. Spitzer M. *The Mind Within the Net.* Cambridge, Mass: The MIT Press; 1999.
33. Garety P, Kuipers E, Fowler D, Freeman D, Bebbington P. A cognitive model of the positive symptoms of psychosis. *Psychol Med.* 2001;31:189–195.
34. Jobe T, Harrow M. Delusions. In: Kadzin A, ed. *Encyclopedia of Psychology.* New York, NY: Oxford University Press; 2000:467–469.
35. Harrow M, Jobe T. Factors involved in outcome and recovery in schizophrenia patients not on antipsychotic medications: a 15-year multi-followup study. *J Nerv Ment Dis.* 2007;195:406–414.
36. Harrow M, Goldberg J, Grossman L, Meltzer H. Outcome in manic disorders: a naturalistic followup study. *Arch Gen Psychiatry*. 1990;47:665–671.
37. Carone J, Harrow M, Westermeyer J. Posthospital course and outcome in schizophrenia. *Arch Gen Psychiatry*. 1991;48:247–253.
38. Harrow M, Sands J, Silverstein M, Goldberg J. Course and outcome for schizophrenia vs other psychotic patients: a longitudinal study. *Schizophr Bull.* 1997;23:287–303.
39. Harrow M, Grossman L, Herbener E, Davis E. Ten-year outcome: patients with schizoaffective disorders, schizophrenia, affective disorders, and mood-incongruent psychotic symptoms. *Br J Psychiatry*. 2000;177:421–426.
40. Harrow M, Herbener E, Shanklin A, Jobe J, Rattenbury F, Kaplan K. Followup of psychotic outpatients: dimensions of delusions and work functioning in schizophrenia. *Schizophr Bull.* 2004;30:147–161.
41. Harrow M, Grossman L, Jobe T, Herbener E. Do patients with schizophrenia ever show periods of recovery? A 15 year multi-followup study. *Schizophr Bull.* 2005;31:723–734.
42. Endicott J, Spitzer R. A diagnostic interview. *Arch Gen Psychiatry*. 1978;35:837–844.
43. Grinker R, Harrow M. *Clinical Research in Schizophrenia: A Multidimensional Approach.* Springfield, Ill: Thomas CC; 1987.
44. McGrath J. Myths and plain truths about schizophrenia epidemiology—the NAPR lecture 2004. *Acta Psychiatr Scand.* 2005;111:4–11.
45. Harrow M, Rattenbury F, Stoll F. Schizophrenic delusions: an analysis of their persistence, of related premorbid ideas, and of three major dimensions. In: Oltmanns T, Maher B, eds. *Delusional Beliefs: Interdisciplinary Perspectives.* New York, NY: John Wiley & Sons, Inc; 1988:185–211.
46. Marengo J, Harrow M, Herbener E, Sands J. A prospective longitudinal 10-year study of schizophrenia's three major factors and depression. *Psychiatry Res.* 2000;97:61–77.
47. Silverstein M, Harrow M. Schneiderian first rank symptoms in schizophrenia. *Arch Gen Psychiatry*. 1981;38:288–293.

48. Gorham D. Proverbs test for clinical and experimental use. *Psychol Rep Monogr*. 1956;suppl 11–12.
49. Goldstein K, Scheerer M. Abstract and concrete behavior: an experimental study with special tests. *Psychological Monographs*. 1941;53:1–151.
50. Wechsler D. *Weschler Adult Intelligence Scale Manual.* New York, NY: Psychological Corporation; 1955.
51. Harrow M, Quinlan D. *Disordered Thinking and Schizophrenic Psychopathology.* New York, NY: Gardner Press; 1985.
52. Sponheim S, Surerus-Johnson C, Leskela J, Dieperink M. Proverb interpretation in schizophrenia: the significance of symptomatology and cognitive processes. *Schizophr Res.* 2003;65:117–123.
53. Harrow M, Grossman L, Silverstein M, Meltzer M, Kettering R. A longitudinal study of thought disorder in manic patients. *Arch Gen Psychiatry*. 1986;43:781–785.
54. Marengo J, Harrow M. The longitudinal courses of thought disorder in schizophrenia and schizoaffective disorder. *Schizophr Bull.* 1997;23:273–285.
55. Racenstein J, Penn D, Harrow M, Schlessor R. Thought disorder and psychological functioning in schizophrenia: concurrent and predictive relationships. *J Nerv Ment Dis.* 1999;187:281–289.
56. Holinger D, Shenton M, Wible C, et al. Superior temporal gyrus volume abnormalities and thought disorder in left-handed schizophrenic men. *Am J Psychiatry*. 1999;156:1730–1735.
57. Landre N, Taylor M. Formal thought disorder in schizophrenia: linguistic, attentional, and intellectual correlates. *J Nerv Ment Dis.* 1995;183:673–680.
58. Harrow M, O'Connell E, Herbener E, Altman A, Kaplan K, Jobe T. Disordered verbalizations in schizophrenia: a speech disturbance or thought disorder? *Compr Psychiatry*. 2003;44:353–359.
59. Harrow M, Jobe T, Herbener E, Goldberg J, Kaplan K. Thought disorder in schizophrenia: working memory and impaired context. *J Nerv Ment Dis.* 2004;192:3–11.
60. Strauss J, Carpenter W. The prediction of outcome in schizophrenia: I. Characteristics of outcome. *Arch Gen Psychiatry*. 1972;27:739–746.
61. Racenstein J, Harrow M, Reed R, Martin E, Herbener E, Penn D. The relationship between positive symptoms and instrumental work functioning in schizophrenia: a 10-year followup study. *Schizophr Res.* 2002;56:95–103.
62. Vaillant G. Prospective prediction of schizophrenic remission. *Arch Gen Psychiatry*. 1964;11:509–518.
63. Vaillant G. A 10-year followup of remitting schizophrenics. *Schizophr Bull.* 1978;4:78–85.
64. Stephens JH. Long-term prognosis and followup in schizophrenia. *Schizophr Bull.* 1978;4:25–47.
65. Stephens J, Pascal R, McHugh P. Long-term follow-up of patients hospitalized for schizophrenia, 1913 to 1940. *J Nerv Ment Dis.* 1997;185:715–721.
66. Westermeyer J, Harrow M. Prognosis and outcome using broad DSM-II and narrow DSM-III concepts of schizophrenia. *Schizophr Bull.* 1984;10:624–637.
67. Zigler E, Levine J. Hallucinations vs. delusions: a developmental approach. *J Nerv Ment Dis.* 1983;171:141–146.
68. Zigler E, Glick M. The developmental approach to adult psychopathology. *Clin Psychol.* 2001;54:2–11.
69. Westermeyer J, Harrow M. Predicting outcome in schizophrenics and nonschizophrenics of both sexes: the Zigler-Phillips social competence scale. *J Abnorm Psychol.* 1986;95:406–409.
70. Bola J. Medication-free research in early episode schizophrenia: evidence of long-term harm? *Schizophr Bull.* 2006;32:288–296.
71. Calton T, Ferriter M, Huband N, Spandler H. A systematic review of the soteria paradigm for the treatment of people diagnosed with schizophrenia. *Schizophr Bull.* 2008; 34:181–192.
72. Fenton W, McGlashan T. Sustained remission in drug-free schizophrenic patients. *Am J Psychiatry*. 1987;144: 1306–1309.
73. Sacks M, Carpenter W, Strauss J. Recovery from delusions: three phases documented by patient's interpretation of research procedures. *Arch Gen Psychiatry*. 1974;30:117–120.
74. Appelbaum P, Robbins P, Roth L. Dimensional approach to delusions: comparison across types and diagnoses. *Am J Psychiatry*. 1999;156:1938–1943.
75. Kendler K, Masterson C, Ungaro R, Davis K. A family history study of schizophrenia-related personality disorders. *Am J Psychiatry*. 1984;141:424–427.
76. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160:13–23.
77. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis-linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res*. 2005;79:59–68.
78. van der Gaag M. A neuropsychiatric model of biological and psychological processes in the remission of delusions and auditory hallucinations. *Schizophr Bull*. 2006;32:S113–S122.
79. Harrow M, Lanin-Kettering I, Miller J. Impaired perspective and thought pathology in schizophrenic and psychotic disorders. *Schizophr Bull.* 1989;15:605–623.
80. Reed R, Harrow M, Herbener E, Martin E. Executive function in schizophrenia: is it linked to psychosis and poor life functioning? *J Nerv Ment Dis.* 2002;190:725–732.
81. Herbener E, Harrow M. Are negative symptoms associated with functioning deficits in both schizophrenic and nonschizophrenic patients? A ten-year longitudinal analysis. *Schizophr Bull.* 2004;30:813–825.
82. Sands J, Harrow M. Depression during the longitudinal course of schizophrenia. *Schizophr Bull.* 1999;25:157–171.
83. Liddle P. The symptoms of schizophrenia: a re-examination of the positive-negative dichotomy. *Br J Psychiatry*. 1987;151:145–151.
84. Liddle P, Barnes T. Syndromes of chronic schizophrenia. *Br J Psychiatry*. 1990;157:558–561.
85. Lenzenweger M. Examining the underlying structure of schizophrenic phenomenology: evidence for a three-process model. *Schizophr Bull.* 1991;17:515–524.
86. Buchanan R, Carpenter W. Domains of psychopathology: an approach to the reduction of heterogeneity in schizophrenia. *J Nerv Ment Dis.* 1994;182:193–204.
87. Van Os J, Fahy T, Jones P, et al. Psychopathological syndromes in the functional psychoses: associations with course and outcome. *Psychol Med.* 1996;26:161–176.
88. Maher B. Delusions as the products of normal cognitions. In: Oltmanns T, Maher B, eds. *Delusional Beliefs.* New York, NY: Wiley; 1988:333–336.
89. Hanssen M, Krabbendam L, Graaf R, Vollebergh W, Van Os J. Role of distress in delusion formation. *Br J Psychiatry*. 2005;187:55–58.

90. Berner P. Delusional atmosphere. *Br J Psychiatry*. 1991;159: 88–93.
91. Maher B. Anomalous experience and delusional thinking: the logic of explanations. In: Oltmanns T, Maher B, eds. *Delusional Beliefs.* New York, NY: Wiley; 1988:15–33.
92. Sands J, Harrow M. Psychotic unipolar depression at follow-up: factors related to psychosis in the affective disorders. *Am J Psychiatry*. 1994;151:995–1000.
93. Grossman L, Harrow M, Sands J. Features associated with thought disorder in manic patients at 2–4 year follow-up. *Am J Psychiatry*. 1986;143:306–311.
94. Schulze TG, Ohlraun S, Czerski PM, et al. Genotype-phenotype studies in bipolar disorder showing association between the DAOA/G30 locus and persecutory delusions: a first step toward a molecular genetic classification of psychiatric phenotypes. *Am J Psychiatry*. 2005;162:2101–2108.
95. Braff D, Freedman R, Schork N, Gottesman I. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophr Bull.* 2007;33:21–32.
96. Andreasen N, Paradiso S, O'Leary D. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull.* 1998;24:203–218.
97. Freeman D, Garety P. Worry, worry processes and dimensions of delusions: an exploratory investigation of a role for anxiety processes in the maintenance of delusional distress. *Behav Cogn Psychother*. 1999;27:47–62.
98. Freeman D, Garety P, Bentall R. *Persecutory Delusions: Assessment, Theory and Treatment. Oxford: Oxford University Press; In press.*
99. Bentall R, Kinderman P, Kaney S. The self, attributional processes and abnormal beliefs: towards a model of persecutory delusions. *Behav Res Ther.* 1994;32:331–341.
100. Bentall R, Kaney S. Attributional lability in depression and paranoia. *Br J Clin Psychol.* 2005;44:475–488.
101. Blackwood NJ, Howard RJ, Bentall RP, Murray RM. Cognitive neuropsychiatric models of persecutory delusions. *Am J Psychiatry*. 2001;158:527–539.
102. Ongur D, Cullen T, Wolf D, et al. The neural basis of relational memory deficit in schizophrenia. *Arch Gen Psychiatry*. 2006;63:356–365.
103. Danckert J, Saoud M, Maruff P. Attention, motor control and motor imagery in schizophrenia: implications for the role of the parietal cortex. *Schizophr Res.* 2004;70:241–261.
104. Quintana J, Wong T, Ortiz-Portillo E, et al. Prefrontal-posterior parietal networks in schizophrenia: primary dysfunction and secondary compensation. *Biol Psychiatry*. 2003;53:12–24.